REMARKS

Claims 49, 51, 52, 60, 63 and 66 have been cancelled. Claims 30-39, 41-44, 46-48, 61, 62, 64, 65, 67-75, 77, 78, 80, 81 and 83-92 have been amended, and Claims 106-108 have been added to the application. Claims 30-48, 61, 62, 64, 65 and 67-108 are pending.

Claims 30-36, 38, 39, 42, 43, 46, 48, 61, 62, 64, 65, 67-75, 77, 78, 80, 81, 83 and 85-92 have been amended to recite "90% amino acid sequence identity," "human IP-10," "human Mig," and/or to correct certain informalities. Support for the amended claims is found, for example, at page 19, lines 17-20, and page 13, lines 6-17.

Support for amended Claims 37, 41, 44, 47, 84 and new Claims 106-108 is found, for example, at page 12, line 19 through page 13, line 6.

The amended claims and new claims are supported by the application as filed. Therefore, this Amendment adds no new matter.

Examiner Interview

The undersigned thanks the Examiner for conducting a telephonic interview on July 16, 2002, and for indicating that claims as amended herein would receive favorable consideration.

Obviousness-type Double Patenting

Claims 75-79, 81, 82 and 84 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable in view of Claims 31-34 of U.S. Patent No. 6,140,064.

Applicants will consider filing a terminal disclaimer if claims deemed to be conflicting with Claims 31-34 of U.S. Patent No. 6,140,064 are indicated as being allowable.

Rejections Under 35 U.S.C. § 112, First Paragraph

Written Description

Claims 30-52, 60-74, 85-92 and 93-105 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way

as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

In Amendment A filed on December 27, 2001 (Paper No. 8), Applicants argued that the application contains an adequate written description of the claimed subject matter relying on binding precedential decisions (Fiers v. Revel, 25 USPQ2d 1601 (Fed. Cir. 1993); Fiddes v. Baird, 30 USPQ2d 1481 (Bd. Pat. App. & Inter. 1993); University of California v. Eli Lilly and Co., 43 USPQ2d 1398 (Fed. Cir. 1997)), the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement, 66 FR 1099 ("Guidelines") and associated PTO training materials (available on line at http://www.uspto.gov/web/offices/pac/writtendesc.pdf; "Training Matertials"), to support their position. (Paper No. 8 at pages 17-26.)

The Examiner maintains the rejection stating that the rejection might be reconsidered if the claims were amended to include structural limitations similar to those in the examples of the Training Materials. (Office Action at page 4, lines 3-6.)

Claims 30-48, 69-74, 93-98, 106 and 107

Claims 30-48, 69-74, 93-98, 106 and 107 have been amended as suggested by the Examiner. As amended, these claims recite that the CXCR3 protein or ligand binding variant thereof shares at least about 90% amino acid sequence identity with SEQ ID NO:2 and binds at least one chemokine selected from IP-10 and Mig. These claims are supported by an adequate written description for the reasons stated in Amendment A, as evidenced by Example 14 of the written description training materials.

In Example 14, the specification contained an adequate written description of the subject matter of the claim drawn to a genus of proteins defined by function (catalyze the reaction of A → B) and structural features (SEQ ID NO:3 or at least 95% identical to SEQ ID NO:3). Training Materials at 53-55. The specification in Example 14 is said to disclose the actual reduction to practice of SEQ ID NO:3, which is novel and non-obvious. Id. at 54. In addition, the specification and claim are said to reveal that:

1) the genus of proteins that are variants of SEQ ID NO:3 does not have substantial variation because all variants must have at least 95% identity to SEQ ID NO:3 and must have the specified activity; and

2) the single disclosed species (SEQ ID NO:3) is representative of the claimed genus because all members of the claimed genus have at least 95% identity to SEQ ID NO:3 and because an assay suitable for identifying all variants that have the specified activity is disclosed.

Id. at 54-55.

The subject application, like Example 14, contains an adequate written description of the subject matter of Claims 30-48, 69-74, 93-98, 106 and 107, because SEQ ID NO:2 is novel and non-obvious (there are no art rejections), the application discloses and exemplifies several methods for assessing binding to CXCR3 (see, *e.g.*, page 39, line 1 through page 51, line 2, and page 70, line 26 *et seq.*) and describes the broader class of CXCR3 proteins or variants used in the claimed methods by describing a combination of function and structural or physical/chemical features which are sufficient to distinguish the members of the genus from other materials. Applying the analysis from Example 14 of the training materials to the claims of the subject application that recite percent amino acid sequence identity reveals:

1) the claimed genus of CXCR3 proteins or ligand binding variants does not have substantial variation because the claimed CXCR3 proteins or variants must have the specified binding activity and share at least about 90% amino acid sequence identity with SEQ ID NO:2; and

2) the disclosed species of human CXCR3 (SEQ ID NO: 2) is representative of the genus because members of the claimed genus have at least about 90% amino acid sequence identity to SEQ ID NO:2, and assays suitable for identifying CXCR3 proteins or variants that have the specified binding activity are disclosed.

On this basis alone the application satisfies the written description requirement of 35 U.S.C. § 112. However, the specification additionally discloses that CXCR3 is a G protein-coupled receptor and discloses the predicted domain structure of the protein (see Figure 2). This additional disclosure together with the art-recognized importance of the extracellular domains of chemokine receptors in ligand binding (see, *e.g.*, Gayle III *et al.*, Reference AX1, which teaches the importance of the amino-terminal extracellular domain of chemokine receptor IL-8 for ligand binding) adequately correlates receptor structure and ligand binding activity, and further demonstrates to the person of skill in the art that Applicants were in possession of the claimed ligand binding variants.

Reconsideration and withdrawal of the rejection with respect to Claims 30-48, 69-74, 93-98, 106 and 107 is requested.

Claims 85-92, 102-105 and 108

Claims 85-92, 102-105 and 108 recite high stringency conditions and that the encoded CXCR3 protein or variant binds at least one chemokine selected from IP-10 and Mig. These claims are supported by an adequate written description for the reasons stated in Amendment A, as evidenced by Example 9 of the written description training materials.

Example 9 of the training materials relates to written description of claims drawn to nucleic acids that hybridize to a reference nucleic acid under highly stringent conditions and encodes a protein which binds a dopamine receptor and stimulates adenylate cyclase activity. Training Materials at page 35-36. The specification in Example 9 is said to include an example where the complement of SEQ ID NO:1 was used under specified hybridization conditions to isolate additional nucleic acids that encode proteins that bind to a dopamine receptor and stimulate adenylate cyclase activity. Id. at 35. The Example states that "[t]he hybridizing nucleic acids were not sequenced. They were expressed and several were shown to encode proteins that bind to a dopamine receptor and stimulate adenylate cyclase activity. These sequences may or may not be the same as SEQ ID NO:1." Id. (Emphasis added.)

The application in Example 9 contains adequate written description of the claimed subject matter and therefore satisfies the written description requirement of 35 U.S.C. § 112 because:

> [A] person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs. Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.

Id. at 36-37 (Emphasis added).

Applying the analysis from Example 9 of the training materials to the claims of the subject application that recite hybridization conditions reveals:

1) the person of skill in the art would not expect substantial variation among species encompassed by the claimed genus because the high stringency wash conditions recited in the claim yield structurally similar DNAs; and

2) high stringency wash conditions in combination with the coding function of DNA and the level of skill in the art are adequate to allow the person skilled in the art to determine that Applicant was in possession of the claimed invention.

Therefore, like in Example 9 of the training materials, the instant specification provides adequate written description for claims that recite hybridization conditions.

Claims 61, 62, 64, 65, 67, 68 and 99-101

Claims 61, 64, 67 and 99-101 recite that the CXCR3 protein or ligand binding variant thereof is encoded by a nucleic acid sharing at least about 75% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1 and binds at least one chemokine selected from IP-10 and Mig. Claims 62, 65 and 68 recite that the CXCR3 protein or ligand binding variant thereof is encoded by a nucleic acid sharing at least about 90% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1. Claims 61, 62, 64, 65, 67, 68 and 99-101 are supported by adequate written description for the reasons stated above with respect to claims that recite amino acid sequence identity and/or claims that recite hybridization conditions. Specifically, the claimed genus does not have substantial variation because the CXCR3 proteins or variants are encoded by a nucleic acid having at least about 75% or at least about 90% nucleotide sequence identity with the coding region of SEQ ID NO:1, and have the specified binding activity. The disclosed species of human CXCR3 is representative of the genus because the members of the claimed genus are encoded by a nucleic acid having at least about 75% or at least about 90% nucleotide sequence identity with the coding region of SEQ ID NO:1, and assays suitable for identifying CXCR3 proteins or variants that have the specified binding activity are disclosed.

In addition, the disclosed domain structure of CXCR3 together with the art-recognized importance of the extracellular domains of chemokine receptors in ligand binding adequately correlates receptor structure and ligand binding activity, and further demonstrates to the person of skill in the art that Applicants were in possession of the claimed ligand binding variants.

Reconsideration and withdrawal of the rejection with respect to Claims 61, 62, 64, 65, 67, 68 and 99-101 is requested.

Enablement

Claims 30-52, 60-74 and 85-105 are rejected under 35 U.S.C. § 112, first paragraph, as failing to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the claimed invention. The Examiner maintains the rejection essentially for the reasons of record stating that the claims "encompass a very large number of possible members of the genus," and that there is "insufficient guidance provided to indicate which amino acid residues are necessary for the CXCR3 function of binding IP-10 and Mig." (Office Action at page 5, lines 13-16.)

Applicants request reconsideration. The claims are enabled if the person of skill in the art could make and use the claimed invention without undue experimentation. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. at 1404. Accordingly, enablement does not require absolute predictability, but that the person of ordinary skill in the art be able to practice the invention without undue experimentation. Id.

The person of ordinary skill in the art would be able to practice the claimed invention following the teachings and guidance of the specification and using no more than routine experimentation. Methods suitable for preparing ligand binding variants and functional variants of proteins that contain amino acid additions, deletions and/or substitutions were well known in the art at the time the application was filed. In addition, the specification discloses and exemplifies methods for identifying CXCR3 proteins, ligand binding variants that bind IP-10 and/or Mig and functional variants that bind IP-10 and/or Mig and induce a cellular response. (Specification at page 39, line 1 *et seq.* and page 70, line 26 *et seq.*, for example.) These teachings and exemplification are further bolstered by the teaching that CXCR3 is a G protein-coupled receptor and disclosure of the predicted domain structure of the receptor (specification at page 2, line 22 *et seq.*; page 8, line 22 *et seq.*; and Figure 2), and the art-known structure-function relationship of G protein-coupled receptors. (See, *e.g.*, Gayle III *et al.*, Reference AX1.)

In view of the teachings and guidance in the specification and knowledge in the art, the person of skill in the art could readily prepare CXCR3 proteins or variants, for example, those sharing at least about 90% amino acid sequence identity with SEQ ID NO:2, using conventional techniques. Such CXCR3 proteins or variants can be screened for IP-10 and/or Mig binding

and/or the capacity to induce a cellular response upon ligand or promoter binding using an assay disclosed in the specification or other suitable assay. Screening proteins, such as receptor proteins, to ascertain binding, signaling and/or cellular response function is considered routine in the art of receptor biology, and does not constitute undue experimentation. This routine screening is analogous to the screening of hybridomas to identify those hybridomas that produce a desired antibody which the Wands court determined was not undue experimentation. Id.

Evidence that the preparation of variant proteins containing amino acid substitutions and the screening of such variants for binding function are routine in the art is provided by Cunningham and Wells (Reference AW2, of record). Cunningham and Wells describe a study in which 62 muteins of human growth hormone containing single amino acid replacements were prepared and tested for binding to the human growth hormone receptor. Cunningham and Wells teach:

> Single alanine mutations (62 in total) were introduced at every residue contained within the three discontinuous segments of hGH (residue 2 to 19, 54 to 74, and 167 to 191) that have been implicated in receptor recognition.

(Cunningham and Wells, Abstract, second sentence.)

Thus, Cunningham and Wells specifically selected positions "that have been implicated in receptor recognition" for mutation. Notwithstanding the targeting of the amino acid substitutions to positions implicated in receptor binding, Cunningham and Wells report that "[t]he overall folding of these mutant proteins was indistinguishable from that of the wild-type hGH ...." Id. The results of the study demonstrated that although some mutants had lower affinity for receptor, many of the mutants displayed only minor changes in dissociation constant relative to wildtype (0.34 nM) and some bound with greater affinity. (Cunningham and Wells at Table 1 (see, P2A (0.31 nM), T3A (0.31 nM), L9A (0.32 nM), R19A (0.37 nM), *etc.*) Thus, Cunningham and wells demonstrates that the person of ordinary skill in the art is well equipped to quickly prepare a large variety of mutants without severe impact on tertiary structure, and to assess the mutants for a desired function.

Reconsideration and withdrawal of the rejection are requested.

Information Disclosure Statements

A Supplemental Information Disclosure Statement (SIDS) with form PTO-1449 is being filed herewith. U.S. Patent No. 6,140,064 is listed on the form PTO-1449. The Examiner has rejected the claims under the judicially created doctrine of obviousness-type double patenting over U.S. Patent No. 6,140,064. However, a form PTO-892 listing this patent has not been received.

An Information Disclosure Statement (IDS) was previously filed on August 7, 2000, but initialed copies of the forms PTO-1449 provided with the IDS have not be received.

The Examiner is requested to provide acknowledgment of consideration of the information provided in the IDS and SIDS in the next Office Communication.

Drawing Correction and Formal Drawings

A Transmittal of Proposed Drawing Corrections and New Formal Drawings, with Formal Drawings (sheets 1/4-4/4) was filed on September 25, 2000. Acknowledgment of approval of the proposed corrections in respectfully requested in the next Office Communication.

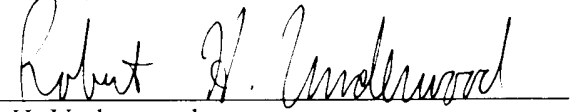
The Office Action included an Attachment for PTO-948 (Rev. 03/01, or earlier). It appears that this attachment was included in error because form PTO-948 was not received with the Office Action and is not indicated as being attached on the Office Action Summary. We assume that no drawing corrections are required.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By 

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

Claims 49, 51, 52, 60, 63 and 66 have been canceled, and new Claims 106-108 have been added to the application.

30. (Three Times Amended) A method of detecting or identifying an agent which binds a mammalian CXC Chemokine Receptor 3 (CXCR3) protein or ligand binding variant thereof, comprising combining an agent to be tested [~~with~~] and a composition comprising an isolated and/or recombinant mammalian CXCR3 protein or ligand binding variant thereof under conditions suitable for binding of ligand to said mammalian CXCR3 protein or ligand binding variant, and detecting or measuring the formation of a complex between said agent and said mammalian CXCR3 protein or ligand binding variant,

wherein said mammalian CXCR3 protein or ligand binding variant selectively binds at least one chemokine selected from the group consisting of IP-10 and Mig, and shares at least about [~~80%~~] 90% amino acid sequence identity with SEQ ID NO:2.

31. (Amended) The method of Claim 30, wherein the agent is a ligand selected from the group consisting of human IP-10[;] and human Mig[~~, a mammalian homolog of IP-10, and a mammalian homolog of Mig~~].

32. (Twice Amended) The method of Claim 31, wherein the ligand is labeled with a label selected from the group consisting of a radioisotope, spin label, antigen label, enzyme label, flourescent group [~~or~~] and chemiluminescent group.

33. (Twice Amended) The method of Claim 30, wherein the assay is a competition assay, in which binding is determined in the presence of one or more ligands selected from the [~~roup~~] group consisting of human IP-10[;] and human Mig[~~, a mammalian homolog of IP-10, and a mammalian homolog of Mig~~].

34. (Three Times Amended) A method of detecting or identifying an agent which binds a mammalian CXCR3 protein or a ligand binding variant thereof comprising:

a) combining an agent to be tested [~~with~~] and a host cell expressing recombinant mammalian CXCR3 protein or a ligand binding variant thereof under conditions suitable for binding of ligand to said mammalian CXCR3 protein or ligand binding variant; and

b) detecting or measuring the formation of a complex between said agent and said mammalian CXCR3 protein or ligand binding variant,

wherein said mammalian CXCR3 protein or ligand binding variant selectively binds at least one chemokine selected from the group consisting of IP-10 and Mig, and shares at least about [~~80%~~] 90% amino acid sequence identity with SEQ ID NO:2.

35. (Amended) The method of Claim 34, wherein the agent is a ligand selected from the group consisting of human IP-10[;] and human Mig[~~, a mammalian homolog of IP-10, and a mammalian homolog of Mig~~].

36. (Amended) The method of Claim 34, wherein the assay is a competition assay, in which binding is determined in the presence of one or more ligands selected from the group consisting of human IP-10[;] and human Mig[~~, a mammalian homolog of IP-10, and a mammalian homolog of Mig~~].

37. (Twice Amended) The method of Claim 34, wherein the mammalian CXCR3 protein or [~~a~~] ligand binding variant thereof can mediate cellular signalling and/or a cellular response, and the formation of a complex is monitored by detecting or measuring a signalling activity or cellular response induced upon ligand binding to [~~of~~] said mammalian CXCR3 protein or ligand binding variant [~~in response thereto~~], wherein said signalling activity or cellular response is selected from the group consisting of a transient rise in the concentration of cytosolic free Ca^{2+} ($[Ca^{2+}]_i$), chemotaxis, exocytosis, degranulation and inflammatory mediator release.

38. (Three Times Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or a ligand binding variant thereof comprising:

a) combining an agent to be tested, [~~with~~] a ligand of said mammalian CXCR3 protein and a composition comprising isolated and/or recombinant mammalian

CXCR3 protein or ligand binding variant thereof under conditions suitable for binding of ligand to said mammalian CXCR3 protein or ligand binding variant; and

b) detecting or measuring the formation of a complex between said mammalian CXCR3 protein or ligand binding variant and said ligand,

[~~whereby~~] wherein inhibition of complex formation by the agent is indicative that the agent is an inhibitor, and

[~~wherein~~] said mammalian CXCR3 protein or ligand binding variant selectively binds at least one chemokine selected from the group consisting of IP-10 and Mig, and shares at least about [~~80%~~] 90% amino acid sequence identity with SEQ ID NO:2.

39. (Twice Amended) The method of Claim 38, wherein the ligand is selected from the group consisting of human IP-10[,] and human Mig[~~, a mammalian homolog of IP-10, and a mammalian homolog of Mig~~].

41. (Three Times Amended) The method of Claim 40, wherein said mammalian CXCR3 protein or ligand binding variant thereof can mediate cellular signalling and/or a cellular response, and the formation of a complex is monitored by detecting or measuring a signalling activity or cellular response induced upon ligand binding to [~~of~~] said mammalian CXCR3 protein or ligand binding variant [~~in response thereto~~], wherein said signalling activity or cellular response is selected from the group consisting of a transient rise in the concentration of cytosolic free Ca^{2+} ($[Ca^{2+}]_i$), chemotaxis, exocytosis, degranulation and inflammatory mediator release.

42. (Three Times Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or ligand binding variant thereof comprising:

a) combining an agent to be tested, [~~with~~] a ligand of said mammalian CXCR3 protein and a host cell expressing a recombinant mammalian CXCR3 protein or ligand binding variant thereof under conditions suitable for binding of ligand to said mammalian CXCR3 protein or ligand binding variant; and

b) detecting or measuring the formation of a complex between said mammalian CXCR3 protein or ligand binding variant and said ligand,

[~~whereby~~] wherein inhibition of complex formation by the agent is indicative that the agent is an inhibitor, and

[~~wherein~~] said mammalian CXCR3 protein or ligand binding variant selectively binds at least one chemokine selected from the group consisting of IP-10 and Mig, and shares at least about [~~80%~~] 90% amino acid sequence identity with SEQ ID NO:2.

43. (Twice Amended) The method of Claim 42, wherein the ligand is selected from the group consisting of human IP-10[;] and human Mig[~~, a mammalian homolog of IP-10, and a mammalian homolog of Mig~~].

44. (Three Times Amended) The method of Claim 42, wherein said mammalian CXCR3 protein or ligand binding variant thereof can mediate cellular signalling and/or a cellular response, and the formation of a complex is monitored by detecting or measuring a signalling activity or cellular response induced upon ligand binding to [~~of~~] said mammalian CXCR3 protein or ligand binding variant [~~in response thereto~~], wherein said signalling activity or cellular response is selected from the group consisting of a transient rise in the concentration of cytosolic free Ca^{2+} ($[Ca^{2+}]_i$), chemotaxis, exocytosis, degranulation and inflammatory mediator release.

46. (Three Times Amended) A method of detecting or identifying an inhibitor of a mammalian CXCR3 protein or functional variant thereof comprising combining an agent to be tested, [~~with~~]

(a) a host cell expressing a recombinant mammalian CXCR3 protein or functional variant thereof, and

(b) a ligand or promoter of said mammalian CXCR3 protein or functional variant, under conditions suitable for detecting a ligand- or promoter-induced response, and assessing the ability of the test agent to inhibit said response,

[~~whereby~~] wherein inhibition of a ligand- or promoter-induced response by the agent is indicative that the agent is an inhibitor, and

[~~wherein~~] said mammalian CXCR3 protein or functional variant selectively binds at least one chemokine selected from the group consisting of IP-10 and Mig, and shares at least about [~~80%~~] 90% amino acid sequence identity with SEQ ID NO:2.

47. (Amended) The method of Claim 46, wherein the response is monitored by detecting or measuring a signalling activity or cellular response of said mammalian CXCR3 protein or functional variant thereof [~~in response thereto~~] induced upon binding of ligand or promoter, wherein said signalling activity or cellular response is selected from the group consisting of a transient rise in the concentration of cytosolic free Ca^{2+} ($[Ca^{2+}]_i$), chemotaxis, exocytosis, degranulation and inflammatory mediator release.

48. (Three Times Amended) A method of detecting or identifying a promoter of a mammalian CXCR3 protein or functional variant thereof comprising combining an agent to be tested [~~with~~] and a host cell expressing a recombinant mammalian CXCR3 protein or functional variant thereof under conditions suitable for detecting a receptor-mediated response, and detecting or measuring said response,

[~~whereby~~] wherein induction or stimulation of said response by the agent is indicative that the agent is a promoter, and

[~~wherein~~] said mammalian CXCR3 protein or functional variant selectively binds at least one chemokine selected from the group consisting of IP-10 and Mig, and shares at least about [~~80%~~] 90% amino acid sequence identity with SEQ ID NO:2.

61. (Twice Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or a ligand binding variant thereof comprising:

a) combining an agent to be tested, [~~with~~] a ligand of said mammalian CXCR3 protein and a composition comprising isolated and/or recombinant mammalian CXCR3 protein or a ligand binding variant thereof under conditions suitable for binding of ligand to said mammalian CXCR3 protein or ligand binding variant; and

b) detecting or measuring the formation of a complex between said mammalian CXCR3 protein or ligand binding variant and said ligand,

[~~whereby~~] wherein inhibition of complex formation by the agent is indicative that the agent is an inhibitor, and

[~~wherein~~] said mammalian CXCR3 protein or ligand binding variant [~~can~~] selectively [~~bind~~] binds at least one chemokine selected from the group consisting of IP-10[~~, Mig, a homolog of IP-10,~~] and [~~a homolog of~~] Mig, and is encoded by a nucleic acid

sharing at least about 75% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1.

62. (Twice Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or a ligand binding variant thereof of Claim 61, wherein said mammalian CXCR3 protein or ligand binding variant is encoded by a nucleic acid sharing at least about 90% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1.

64. (Twice Amended) A method of detecting or identifying an inhibitor of a mammalian CXCR3 protein or functional variant thereof comprising combining an agent to be tested, [~~with~~]

(a) a host cell expressing a recombinant mammalian CXCR3 protein or functional variant thereof, and

(b) a ligand or promoter [~~thereof~~] of said mammalian CXCR3 protein or functional variant, under conditions suitable for detecting a ligand- or promoter-induced response, and assessing the ability of the test agent to inhibit said response, [~~whereby~~] wherein inhibition of a ligand- or promoter-induced response by the agent is indicative that the agent is an inhibitor, and

[~~wherein~~] said mammalian CXCR3 protein or functional variant [~~can~~] selectively [~~bind~~] binds at least one chemokine selected from the group consisting of IP-10[~~, Mig, a homolog of IP-10,~~] and [~~a homolog of~~] Mig, and is encoded by a nucleic acid sharing at least about 75% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1.

65. (Twice Amended) A method of detecting or identifying an inhibitor of a mammalian CXCR3 protein or functional variant thereof of Claim 64, wherein said mammalian CXCR3 protein or functional variant is encoded by a nucleic acid sharing at least about 90% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1.

67. (Twice Amended) A method of detecting or identifying a promoter of a mammalian CXCR3 protein or functional variant thereof comprising combining an agent to be tested [~~with~~] and a host cell expressing a recombinant mammalian CXCR3 protein or functional variant thereof under conditions suitable for detecting a receptor-mediated response, and detecting or measuring said response,

[~~whereby~~] wherein induction or stimulation of said response by the agent is indicative that the agent is a promoter, and

[~~wherein~~] said mammalian CXCR3 protein or functional variant selectively binds at least one chemokine selected from the group consisting of IP-10[~~, Mig, a homolog of IP-10,~~] and [~~a homolog of~~] Mig, and is encoded by a nucleic acid sharing at least about 75% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1.

68. (Twice Amended) A method of detecting or identifying a promoter of a mammalian CXCR3 protein or functional variant thereof of Claim 67, wherein said mammalian CXCR3 protein or functional variant is encoded by a nucleic acid sharing at least about 90% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1.

69. (Twice Amended) A method of detecting or identifying an agent which binds a mammalian CXCR3 protein or ligand binding variant thereof of Claim 30, wherein the mammalian CXCR3 protein or ligand binding variant thereof is a human CXCR3 or ligand binding variant thereof.

70. (Twice Amended) A method of detecting or identifying an agent which binds a mammalian CXCR3 protein or a ligand binding variant thereof of Claim 34, wherein the mammalian CXCR3 protein or ligand binding variant thereof is a human CXCR3 or ligand binding variant thereof.

71. (Twice Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or a ligand binding variant thereof of Claim 38, wherein the

mammalian CXCR3 protein or ligand binding variant thereof is a human CXCR3 or ligand binding variant thereof.

72. (Twice Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or ligand binding variant thereof of Claim 42, wherein the mammalian CXCR3 protein or ligand binding variant thereof is a human CXCR3 or ligand binding variant thereof.

73. (Twice Amended) A method of detecting or identifying an inhibitor of a mammalian CXCR3 protein or functional variant thereof of Claim 46, wherein the mammalian CXCR3 protein or functional variant thereof is a human CXCR3 or functional variant thereof.

74. (Twice Amended) A method of detecting or identifying a promoter of a mammalian CXCR3 protein of functional variant thereof of Claim 48, wherein the mammalian CXCR3 protein or functional variant thereof is a human CXCR3 or functional variant thereof.

75. (Twice Amended) A method of detecting or identifying an inhibitor of ligand binding to a human CXCR3 protein comprising:

a) combining an agent to be tested, [~~with~~] a ligand of said CXCR3 protein and a composition comprising recombinant human CXCR3 protein under conditions suitable for binding of ligand [~~thereto~~] to said human CXCR3 protein; and

b) detecting or measuring the formation of a complex between said human CXCR3 protein and said ligand,

[~~whereby~~] wherein inhibition of complex formation by the agent is indicative that the agent is an inhibitor, and

[~~wherein~~] said human CXCR3 protein selectively binds at least one chemokine selected from the group consisting of human IP-10 or human Mig and comprises the extracellular N-terminal segment of the protein shown in Figure 2 (SEQ ID NO:2).

77. (Amended) The method of Claim 75, [~~wherein the~~] wherein the ligand is labeled with a label selected from the group consisting of a radioisotope, spin label, antigen label, enzyme label, flourescent group [~~or~~] and chemiluminescent group.

78. (Amended) The method of Claim 75, wherein the composition comprising recombinant human CXCR3 protein comprises a membrane fraction of host cells expressing recombinant human CXCR3 protein.

80. (Amended) The method of Claim 79, wherein the ligand is labeled with a label selected from the group consisting of a radioisotope, spin label, antigen label, enzyme label, flourescent group [~~or~~] and chemiluminescent group.

81. (Twice Amended) A method of detecting or identifying an inhibitor of ligand binding to a human CXCR3 protein comprising:

a) combining an agent to be tested, [~~with~~] a ligand of said human CXCR3 protein and a host cell expressing a recombinant human CXCR3 protein under conditions suitable for binding of ligand to said human CXCR3 protein; and

b) detecting or measuring the formation of a complex between said protein and said ligand,

[~~whereby~~] wherein inhibition of complex formation by the agent is indicative that the agent is an inhibitor, and

[~~wherein~~] said human CXCR3 protein selectively binds at least one chemokine selected from the group consisting of human IP-10 or human Mig and comprises the extracellular N-terminal segment of the protein shown in Figure 2 (SEQ ID NO:2).

83. (Amended) The method of Claim 81, [~~wherein the~~] wherein the ligand is labeled with a label selected from the group consisting of a radioisotope, spin label, antigen label, enzyme label flourescent group [~~or~~] and chemiluminescent group.

84. (Amended) The method of Claim 81, wherein the human CXCR3 protein can mediate cellular signaling and/or a cellular response, and the formation of a complex is monitored by detecting or measuring a signaling activity or cellular response of said CXCR3 protein

[~~in response thereto~~] induced upon ligand binding, wherein said signalling activity or cellular response is selected from the group consisting of a transient rise in the concentration of cytosolic free Ca^{2+} ($[Ca^{2+}]_i$), chemotaxis, exocytosis, degranulation and inflammatory mediator release.

85. (Twice Amended) A method of detecting or identifying an agent which binds a mammalian CXCR3 protein or ligand binding variant thereof, comprising combining an agent to be tested [~~with~~] and a composition comprising an isolated and/or recombinant mammalian CXCR3 protein or ligand binding variant thereof under conditions suitable for binding of ligand to said mammalian CXCR3 protein or ligand binding variant, and detecting or measuring the formation of a complex between said agent and said mammalian CXCR3 protein or ligand binding variant,

wherein said mammalian CXCR3 protein or ligand binding variant selectively binds at least one chemokine selected from the group consisting of IP-10[~~, Mig, a homolog of IP-10,~~] and [~~a homolog of~~] Mig, and is encoded by a nucleic acid that hybridizes, under high stringency wash conditions of 2X SSC, 0.1% SDS at room temperature for ten minutes followed by two washes in 1X SSC, 0.1% SDS at 65°C for thirty minutes and a final wash in 0.5X SSC, 0.1% SDS at 65°C for ten minutes, to a nucleic acid selected from the group consisting of:

a) the complement of SEQ ID NO:1; and

b) the complement of a portion of SEQ ID NO:1 comprising the open reading frame.

86. (Twice Amended) A method of detecting or identifying an agent which binds a mammalian CXCR3 protein or ligand binding variant thereof of Claim 85, wherein the mammalian CXCR3 protein or ligand binding variant thereof is a human CXCR3 or ligand binding variant thereof.

87. (Twice Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or a ligand binding variant thereof comprising:

a) combining an agent to be tested, [~~with~~] a ligand of said mammalian CXCR3 protein and a composition comprising isolated and/or recombinant mammalian CXCR3 protein or a ligand binding variant thereof under conditions suitable for

binding of ligand to said mammalian CXCR3 protein or ligand binding variant; and

b) detecting or measuring the formation of a complex between said mammalian CXCR3 protein or ligand binding variant and said ligand,

[~~whereby~~] wherein inhibition of complex formation by the agent is indicative that the agent is an inhibitor, and

[~~wherein~~] said mammalian CXCR3 protein or ligand binding variant selectively binds at least one chemokine selected from the group consisting of IP-10[~~, Mig, a homolog of IP-10,~~] and [~~a homolog of~~] Mig, and is encoded by a nucleic acid that hybridizes, under high stringency wash conditions of 2X SSC, 0.1% SDS at room temperature for ten minutes followed by two washes in 1X SSC, 0.1% SDS at 65°C for thirty minutes and a final wash in 0.5X SSC, 0.1% SDS at 65°C for ten minutes, to a nucleic acid selected from the group consisting of:

i) the complement of SEQ ID NO:1; and

ii) the complement of a portion of SEQ ID NO:1 comprising the open reading frame.

88. (Twice Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or a ligand binding variant thereof of Claim 87, wherein the mammalian CXCR3 protein or ligand binding variant thereof is a human CXCR3 or ligand binding variant thereof.

89. (Twice Amended) A method of detecting or identifying an inhibitor of a mammalian CXCR3 protein or functional variant thereof comprising combining an agent to be tested, [~~with~~]

(a) a host cell expressing a recombinant mammalian CXCR3 protein or functional variant thereof, and

(b) a ligand or promoter [~~thereof~~] of said mammalian CXCR3 protein, under conditions suitable for detecting a ligand- or promoter-induced response, and assessing the ability of the test agent to inhibit said response,

[~~whereby~~] wherein inhibition of a ligand- or promoter-induced response by the agent is indicative that the agent is an inhibitor, and

[~~wherein~~] said mammalian CXCR3 protein or functional variant selectively binds at least one chemokine selected from the group consisting of IP-10[~~, Mig, a homolog of IP-10,~~] and [~~a homolog of~~] Mig, and is encoded by a nucleic acid that hybridizes, under high stringency wash conditions of 2X SSC, 0.1% SDS at room temperature for ten minutes followed by two washes in 1X SSC, 0.1% SDS at 65°C for thirty minutes and a final wash in 0.5X SSC, 0.1% SDS at 65°C for ten minutes, to a nucleic acid selected from the group consisting of:

i) the complement of SEQ ID NO:1; and

ii) the complement of a portion of SEQ ID NO:1 comprising the open reading frame.

90. (Twice Amended) A method of detecting or identifying an inhibitor of a mammalian CXCR3 protein or functional variant thereof of Claim 89, wherein the mammalian CXCR3 protein or <u>functional</u> variant thereof is a human CXCR3 or functional variant thereof.

91. (Twice Amended) A method of detecting or identifying a promoter of a mammalian CXCR3 protein or functional variant thereof comprising combining an agent to be tested [~~with~~] <u>and</u> a host cell expressing a recombinant mammalian CXCR3 protein or functional variant thereof under conditions suitable for detecting a receptor-mediated response, and detecting or measuring said response,

[~~whereby~~] <u>wherein</u> induction or stimulation of said response by the agent is indicative that the agent is a promoter, <u>and</u>

[~~wherein~~] said mammalian CXCR3 protein or functional variant selectively binds at least one chemokine selected from the group consisting of IP-10[~~, Mig, a homolog of IP-10,~~] and [~~a homolog~~] Mig, and is encoded by a nucleic acid that hybridizes, under high stringency wash conditions of 2X SSC, 0.1% SDS at room temperature for ten minutes followed by two washes in 1X SSC, 0.1% SDS at 65°C for thirty minutes and a final wash in 0.5X SSC, 0.1% SDS at 65°C for ten minutes, to a nucleic acid selected from the group consisting of:

i) the complement of SEQ ID NO:1; and

ii) the complement of a portion of SEQ ID NO:1 comprising the open reading frame.

92. (Twice Amended) A method of detecting or identifying a promoter of a mammalian CXCR3 protein [~~of~~] or functional variant thereof of Claim 91, wherein the mammalian CXCR3 protein or functional variant thereof is a human CXCR3 or functional variant thereof.